REMARKS

Amendments to the Specification

Applicants amend the specification herein to correct spelling of the word "van der Waals". Applicants respectfully submit that one of ordinary skill in the art would understand both that the spelling found in the specification as filed is both in error and that the amended form presented herein is the proper spelling. Accordingly, no new matter is introduced by way of this amendment, and entry thereof is respectfully requested.

Amendments to the claims

Claims 3, 5, 8, 15, 29, 43, and 44 are canceled without prejudice or disclaimer. Applicants reserve the right to file a continuation application or to take such other action as would be appropriate to preserve their rights to the canceled subject matter.

Applicants also take this opportunity to amend claims 1, 2, 4, 6, 9, 12 – 14, 31, 36, 37, 41, 42, 45, 46, and 47, to more particularly recite that which they consider to be inventive subject matter claimed.

Claim 1 is amended to recite "applying a coarse-grained docking algorithm" (see, *e.g.*, specification at page 15, ¶ [0032]). Claim 1 is further amended to recite "selecting best conformations", and "optimizing the best conformations using molecular mechanics", as discussed in the specification as filed at, *e.g.*, pages 17 – 18, ¶ [0035] and FIG. 2.

Claim 1 is additionally amended to recite minimizing a preferred set of conformations (see, *e.g.*, specification at last line of page 21, last line of ¶ [0040]).

Claim 1 is also amended to recite outputting a data file, support for which is found in the specification as filed at ¶ [0035].

Claim 5 is amended to recite further operations, as described in the specification as filed at for example paragraph [0034].

Claims 31 and 36 are likewise amended.

Claims 46 and 47 are amended to place them in dependent form.

Claim 31 is amended to delete the term "on a computer readable medium" and append the clause "wherein the computer program product is tangibly embodied in a machine-readable storage device for execution by a programmable processor" as supported, for example, in the specification at page 41, lines 5-8 (paragraph [0087]) which states in pertinent part "[a]pparatus of the invention can be implemented in a computer program product tangibly embodied in a machine-readable storage device for execution by a programmable processor."

Other amendments are made throughout the claims to correct clerical errors, or to clarify antecedent basis and thereby render their language consistent with the foregoing amendments to claims from which the depend.

New claims 48 – 55 are introduced herein, and are supported as follows.

Claim 48 recites a system for identifying one or more ligand conformations that bind to a protein. Support for such a computer system is found throughout the specification as filed, and particularly at, *e.g.*, FIG. 3 (and accompanying description in paragraph [0037] on page 19).

Claim 49, depending from claim 48, recites limitations also found in claims 46 and 47 prior to amendment herein, and is, therefore also properly supported.

Claims 50 – 52 recite exemplary all-atom force fields, referenced in the specification as filed at, *e.g.*, pages 4 (in ¶ [0007]), and 21 (bottom of ¶ [0040]).

Claims 53 – 55 recite the Monte Carlo class of algorithms, referenced in the specification as filed at, *e.g.*, page 15 (in ¶ [0032]).

No new matter is added by way of these amendments and, accordingly, entry thereof is respectfully requested.

Rejection under 35 U.S.C. § 101

Claims 29, 31, 36-45, 46 and 47 stand rejected under 35 U.S.C. § 101 as allegedly being drawn to non-statutory subject matter. The following remarks address the rejections of these claims in the order referenced in the Office Action.

Rejection of Claim 29 under 35 U.S.C. § 101

The Examiner alleges that claim 29 is directed to non-functional descriptive material. Because Applicants have canceled claim 29 with the instant amendment, its rejection under 35

U.S.C. § 101 is moot. Accordingly, Applicants respectfully request withdrawal of the corresponding rejection.

Rejection of Claim 46 under 35 U.S.C. § 101

The Examiner alleges that claim 46 is non-statutory because it does not recite an actual, concrete result. In reference to the additional rejection of claim 46 under 35 U.S.C. § 112 for alleged indefiniteness, the Examiner also states that the actual result of the claimed method is unclear.

Applicants have amended claim 46 herein to depend from claim 1. Furthermore, as discussed further herein in connection with the rejections under 35 U.S.C. § 112, Applicants have clarified the result of the outputting step of claim 1 as producing a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies. Applicants respectfully contend that the preceding amendment provides the clarification requested by the Examiner and also, simultaneously, addresses the rejection of claim 46 under 35 U.S.C. § 101.

Furthermore, claim 46 recites statutory subject matter under 35 U.S.C. § 101 because the data file provided by the outputting step is a useful, concrete and tangible result. Courts have found algorithmic methods which produce a useful, concrete and tangible result to be statutory subject matter under 35 U.S.C. § 101. The standard of patentability for such inventions was set forth in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.* 149 F.3d 1368 (Fed. Cir. 1998) which held that:

> [T]he transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces 'a useful, concrete and tangible result' — a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.

Therefore, an algorithmic method that generates a useful, concrete and tangible result is statutory subject matter under 35 U.S.C. § 101 when the method transforms data into a calculated value (or values), momentarily fixed for recording and reporting purposes, *e.g.*, in an output data file.

Moreover, a factor which supports finding a useful, concrete and tangible result is, according to *State Street Bank*, acceptance, use, or reliance on the calculated value by persons of ordinary skill in the art.

Claim 46 recites statutory subject matter because it mathematically transforms protein and ligand structural data and outputs a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies, where the data file is momentarily fixed for recording and reporting purposes. This data file can be used, and the information it contains accepted and relied upon, by one of ordinary skill in the art.

Furthermore, the data file represents a useful result because it corresponds to descriptions of physical interactions between ligands and proteins. Medicinal chemists, for example, can use the data file to screen large numbers of drug candidates *in silico* without laborious and expensive experimentation. Chemists, for example, may evaluate large numbers of proposed new ligands to identify specific candidates for synthesis and testing without the burden of first synthesizing a large library of ligands. Consequently, because claim 46 meets the test set forth in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, claim 46 is drawn to statutory subject matter under 35 U.S.C. § 101. Applicants respectfully request that the rejection of Claim 46 be withdrawn.

Rejection of Claims 31, 36-45 and 47 under 35 U.S.C. § 101

The Examiner alleges that claims 31, 36-45 and 47 are not statutory subject matter because a "computer readable medium encompasses non-physical media, such as carrier waves," and "because the computer readable medium is not defined by the specification to be a physical object." Applicants respectfully disagree.

Because Applicants have canceled claims 43 and 44, their rejection under 35 U.S.C. § 101 is moot.

Claims 31, 36-42 and 47, as amended herein, are directed in part to a "a computer program product tangibly embodied in a machine-readable storage device for execution by a programmable processor" as supported, for example in the specification at page 41, lines 5-8

(paragraph [0087]). Applicants respectfully submit that this element of the claim alone rebuts the Examiner's rejection.

Nevertheless, Applicants both disagree that one of ordinary skill in the art would not appreciate what Applicants mean by a computer program product, and that, even if such a definition does in fact encompass non-physical media, that fact alone supports a finding of non-statutory subject matter.

Applicants' specification describes "mass storage devices for storing data files" as follows (paragraph [0089], page 42):

> "[s]torage devices suitable for tangibly embodying computer program instructions and data include all forms of non-volatile memory, including by way of example semiconductor memory devices, such as EPROM, EEPROM, and flash memory devices; magnetic disks such as internal hard disks and removable disks; magneto-optical disks; and CD-ROM disks. Any of the foregoing can be supplemented by, or incorporated in, ASICs (application-specific integrated circuits)."

Thus, by the plain language of the claims as amended herein, as well as by exemplary description in the specification as filed, Applicants' claimed invention is a product, a tangible medium, and not something that is non-physical.

Consequently, the Examiner's rejection of claims 31, 36-45 and 47 under 35 U.S.C. § 101 is overcome and its withdrawal is respectfully requested.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 46 and 47 stand rejected under 35 U.S.C. § 112 (second paragraph) as allegedly being indefinite. The Examiner alleges that the scoring function groups are not clearly delineated and that the results of the outputting step in each claim are not clear.

Applicants have amended the claims by enumerating the scoring function groups. For example, claim 46 recites in part:

> a scoring function selected from the group consisting of
> (i) subtracting the free energy of the conformation in water from the energy of the conformation in the protein; and
> (ii) subtracting a sum of the free energy of the protein and a free energy of the conformation from a free energy of the conformation in the protein.

Consequently, the scoring function is clarified as being selected from the group consisting of the two subtracting steps enumerated by (i) and (ii). Claim 47 is likewise amended.

Further, as noted above, the result of the outputting step in claim 46 as amended herein to depend from claim 1 is a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies. The outputting step in claim 31 from which claim 47 depends is similarly amended herein.

Accordingly, Applicants respectfully contend that the preceding amendments provide the clarification requested by the Examiner. Consequently, Applicants respectfully request withdrawal of the corresponding rejections under 35 U.S.C. § 112 second paragraph.

Rejections under 35 U.S.C. § 102(b)

Claims 1-4, 8, 9, 11, 12, 16, 29, 31, 36, 37, 39, 40, 46 and 47 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by DeWitte and Shakhnovich, *J. Am. Chem. Soc.*, 1996, volume 118, pages 11733-11744 ("DeWitte", hereinafter). The Examiner alleges that Dewitte teaches the steps of the claimed invention. Applicants respectfully traverse the rejection because DeWitte does not teach every element of Applicants' claimed invention. [1]

The law requires that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Moreover, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Thus, a reference that fails to expressly or inherently describe even one of the elements as set forth in the claim does not describe the identical invention in complete detail as contained in the claim.

Because, as elaborated upon herein, DeWitte does not expressly or inherently describe the entirety of Applicants' claim, including the particular claimed step of annealing molecular

---

[1] Applicants arguments herein are based on claims as amended herein and on the assumption that those amendments will be entered by the Examiner. Nevertheless, Applicants expressly deny that DeWitte anticipates Applicants' claims as pending prior to entry of the instant amendments.

dynamics optimization identified by the Examiner, Applicants' claimed invention is not anticipated by Dewitte.

Applicants' claims as amended herein comprise a method of identifying one or more ligand conformations that bind to a protein (Claim 1), corresponding instructions for performing that method (Claim 31), and a system configured to carry out such a method (Claim 49). The method of amended claim 1 is representative, and recites a method of identifying one or more ligand conformations that bind to a protein. In clean form, the method of claim 1 as amended herein comprises the following steps:

> obtaining structural information for the protein and for one or more ligands;
> identifying at least one binding region of the protein;
> applying a coarse-grained docking algorithm to identify a plurality of binding
>   conformations for the one or more ligands in the binding region;
> selecting best conformations from the binding conformations for the one or more
>   ligands;
> optimizing the best conformations using molecular mechanics;
> using annealing molecular dynamics including solvation effects to further
>   optimize a subset of the best conformations;
> minimizing a preferred set of conformations from the subset of the best
>   conformations;
> calculating a binding energy for each conformation of the preferred set of
>   conformations;
> ranking the conformations of the preferred set of conformations based on the
>   calculated binding energies;
> selecting for each of the one or more ligands the conformation of the preferred set
>   of conformations having the lowest calculated binding energy; and
> outputting a data file comprising a list of selected ligand-protein conformations
>   having the lowest calculated binding energy, and their respective binding
>   energies.

Each selected ligand-protein conformation and its respective energy in the output data file is a product of the claimed steps beginning with structural information for the protein and one or more ligands. These steps also embody an increasing level of complexity of calculation at each step, beginning with coarse-grained docking and proceeding through a molecular mechanics optimization, optimization using annealing molecular dynamics including solvation effects, and a second optimization prior to concluding with a ranking based on the calculated binding energies.

DeWitte Describes a Small Molecule Growth Algorithm

DeWitte's Small Molecule Growth algorithm ('SMoG') grows simple organic molecules directly into a binding region of a protein molecules by joining fragments with single bonds (DeWitte at p. 11736, col. 1, lines 10-12). The essence of DeWitte's energy calculations is shown at p. 11736, col. 1, lines 28 – 60. Each added fragment is torsionally rotated at fixed increments, and all rotamers, except those sterically hindered, are evaluated, whereupon the lowest energy rotamer is considered as a candidate for acceptance. (*Id.* at p. 11736, col. 1, lines 28-34). Acceptance is determined by a Metropolis Monte Carlo criterion, where the new energy per atom of the present molecule is compared with that of the preceding molecule before addition of a fragment in the present growth step. (*Id.* at p. 11736, col. 1, lines 34-36). Every fragment addition resulting in a decrease in energy per atom is accepted and every fragment addition resulting in an increase in energy per atom is only accepted if the increase is less than the Metropolis Monte Carlo criterion. (*Id.* at p. 11736, col. 1, ll. 36-39). Therefore, DeWitte uses a single energy calculation step, a free energy calculation to determine a best rotamer of a given molecular structure, without a sequence of minimizations of conformational energies.

Dewitte Does Not Teach Applicants' Claimed Invention

Accordingly, DeWitte does not describe the claimed sequence of steps. As described hereinabove, Dewitte's SMoG algorithm describes a growth step, a rotamer energy ranking step, and a Metropolis Monte Carlo comparison between a rotamer configuration of a current molecule and a molecule at an immediately preceding growth step.

DeWitte does not teach at least the following aspects of Applicants' claimed invention: optimizing a selection of best conformations of ligands using molecular mechanics; and using annealing molecular dynamics including solvation effects to further *optimize* a subset of the best conformations. Accordingly, because Dewitte does not describe the entire sequence of steps as claimed, Dewitte does not anticipate the claimed invention.

DeWitte Does Not Disclose the Claimed Annealing Molecular Dynamics Optimization Step

Applicants' claimed method recites using annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations. The Metropolis Monte

Carlo criterion taught by DeWitte is a method of selecting between two different branches of DeWitte's Small Molecule Growth algorithm by comparing two predetermined, static configurations of two different molecules. These two molecules, the lowest energy rotamer of the present growth step and the lowest energy rotamer of the previous growth step, are different molecules from one another because of the molecular fragment added in the growth step. Moreover, the conformations of these different molecules are static, being determined in the preceding step of fragment rotation and lowest energy rotamer selection, and are not optimized by the Metropolis Monte Carlo acceptance criterion. Thus, the Monte Carlo method of DeWitte involves no optimization of conformations of a particular ligand. The Metropolis Monte Carlo criterion described by DeWitte is merely a yardstick to select between two different branches of the growth algorithm and consequently is not a method of optimization.

Moreover, there is no teaching elsewhere in DeWitte of whether or how to optimize a configuration of a molecule using the Metropolis Monte Carlo criterion to result in a new, optimized configuration of that molecule. Thus, DeWitte does not describe the claimed step of using annealing molecular dynamics including solvation effects to further optimize a subset of best conformations of a population of molecules.

Consequently, because DeWitte does not describe the step of using annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations, let alone the entire sequence of steps as claimed, DeWitte does not anticipate the claimed invention. Applicants respectfully request withdrawal of the corresponding rejection of claims 1 – 4, 8, 9, 11, 12, 16, 29, 31, 36, 37, 39, 40, 46 and 47 under 35 U.S.C. § 102(b). Furthermore, because claims 3, 8, and 29 have been canceled herein, their rejection is moot.

Rejections under 35 U.S.C. § 102(e)(1)

Claims 1-4, 6, 9, 11, 12, 31, 36, 37, 39, 40, 41, 43, 44 and 45 stand rejected under 35 U.S.C. § 102(e)(1) as allegedly being anticipated by Freire and Luque, U.S. Pub. App. No. 2001/0000807, now U.S. 6,772,073 ("Freire" hereinafter).

As noted hereinabove, the law requires that each and every element as set forth in the claim must be expressly or inherently described in a single prior art reference in order for that

reference to anticipate the claim. Applicants have previously argued (Response, April 28, 2006) that Freire does not anticipate the claimed invention because there is no teaching of the claimed optimizing step using annealing molecular dynamics. Applicants argued that the Examiner's previous assertion of equivalence between structure-based thermodynamic analysis and annealing molecular dynamics was neither supported by Freire nor scientifically correct. Applicants provided a definition of "simulated annealing," (an example of an annealing method) explaining that it is a particular combinatorial optimization method and is not anticipated by the term "structure-based thermodynamic analysis" in Freire. Moreover, Applicants noted that Freire does not disclose any kind of annealing method for optimization, including annealing molecular dynamics.

As the Examiner now acknowledges, Freire does not recite "simulated annealing" (July 28, 2006 Office Action, page 6). In fact, Freire does not recite any of the terms anneal, annealing, or annealing molecular dynamics. Consequently, there is no express description of annealing molecular dynamics in Freire. The key distinction between the teachings of Freire and Applicants' claimed invention is that Freire teaches no optimization of conformational structure using an annealing method. The only portion of Freire that references identifying a conformation with the lowest energy is on page 9, right hand column, item 12. This section describes using an energy function and a minimization algorithm, but does not reference an annealing method. The mere fact that the energy function referenced by Freire is based on free energy terms is *not* equivalent to use of an annealing, or molecular dynamics-based method.

If, on the other hand, the Examiner believes that Freire *inherently* describes annealing molecular dynamics, the burden of proof is on the Examiner: "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). See also M.P.E.P., § 2112. However, in the July 28, 2006 Office Action, the Examiner alleges only that Freire "disclose(s) a novel algorithm (Woolford) that incorporate [*sic*] a combination of identification, optimization and selection steps to design ligands with optimal

binding affinities." This statement provides no basis in fact or technical reasoning why such disclosures of Freire are relevant to annealing methods, and certainly does not explain how Freire allegedly discloses Applicants' claimed step of using annealing molecular dynamics including solvation effects to further optimize a subset of best ligand conformations.

Therefore, because the Examiner agrees that the claimed step of optimizing using annealing molecular dynamics is not expressly described, and the Examiner does not demonstrate how this claimed step is inherently expressed, the rejection of claims 1-4, 6, 9, 11, 12, 31, 36, 37, 39, 40, 41, 43, 44 and 45 under 35 U.S.C. § 102(e)(1) over Freire is improper. Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 103 (a)

Claims 1-6, 8-12, 15, 16, 29, 31, 36-40 and 43-45 stand rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Zuo, *et al.* (1998) further in view of DeWitte.

Applicants' previous reply assumed that Zuo, *et al.* (1998) referred to Zou, X., *et al.*, *J. Am. Chem. Soc.* (1999) volume 121, pages 8033-8043 ("Zou (1999)"), as Applicants are not aware of any "Zuo, *et al.* (1998)" reference cited in the file history. Because the Examiner has maintained the rejection, once again citing Zuo, *et al.* (1998) but without further clarifying or correcting the exact citation, Applicants remain uncertain which reference underlies the rejection, now reiterated in the July 28, 2006 Office Action. Applicants respectfully again request that the Examiner confirm the corresponding citation. Applicants' arguments herein are based on Zou (1999).

To establish a prima facie case of obviousness, all of the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

As discussed hereinabove, DeWitte fails to teach at least two steps of Applicants' claimed invention. The deficiencies of DeWitte are not provided by Zou (1999).

In particular, Zou (1999) does not teach or suggest the use of annealing molecular dynamics. Zou (1999) describes the use of the Generalized-Born (GB/SA) model of solvation to estimate ligand binding energies, through modifications of the model to account for electrostatic interactions between the ligand and the solvent, and introduces a formula to estimate the binding

free energy by calculating a free energy score. For similar considerations as discussed in connection with Freire, mere description of free energy estimations is not equivalent to an annealing calculation. Zou (1999) is silent in respect of annealing molecular dynamics. Consequently, Zou (1999) does not teach at least one of Applicants' claimed sequence of steps.

Accordingly, since Zou (1999) does not teach or suggest the particular claimed step of using annealing molecular dynamics including solvation effects to further optimize a subset of the best conformations, it does not provide teachings missing from DeWitte as detailed above. Therefore the claimed invention is not obvious over a combination of Zou (1999) and DeWitte.

Dependent claims are nonobvious under 35 U.S.C. § 103 "if the independent claims from which they depend are nonobvious." In re Fine 837 F.2d 1071; 5 USPQ.2d 1596; MPEP 2143.03.

For at least these reasons, the claimed invention is not obvious over Zou (1999) in view of DeWitte, and Applicants respectfully request withdrawal of the corresponding rejections of claims 1 – 6, 8 – 12, 15, 16, 29, 31, 36 – 40, and 43 – 45 under 35 U.S.C. § 103 (a) over Zou (1999) in view of DeWitte. Applicants note that claims 3, 5, 8, 15, 29, 43, and 44 are cancelled herein, thereby mooting their rejection under 35 U.S.C. § 103.

REQUEST FOR TELEPHONIC INTERVIEW

Applicants' Attorney requests a telephonic interview with the Examiner and his supervisor at such time as the Examiner is next preparing to act on this application, and prior to issue of the Examiner's next action.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5005.

No fee is believed to be due. If, however, there are any charges or credits, please apply them to Deposit Account No. 06-1050.

Respectfully submitted,

Date: *December 28, 2006*

Richard G. A. Bone
Richard G. A. Bone
Reg. No. 56,637

Customer No. 26181
Fish & Richardson P.C.
Telephone: (650) 839-5070
Facsimile: (650) 839-5071

50365260.doc